Remarks

Claims 25-45 are pending in the application.

Claims 26, 38, and 44 have been editorially amended. No issues of new matter arise, and entry of the amendment is respectfully requested.

Rejection under 35 USC § 103

Claims 25-45 are rejected under 35 USC § 103 as being obvious over WO 98/39000 in view of US Patent No. 5,278,176 to Lin (hereafter "Lin") or Buccafusco et al, *Brain Research*, 852:76-83 (2000) (hereafter "Buccafusco").

Applicants respectfully traverse the rejection.

WO 98/39000 describes the compounds of the claimed invention, i.e., donepezil and compounds of Formula (I). However, WO 98/39000 does not disclose or suggest (i) a method for treating substance abuse in a patient in need thereof comprising administering a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof.

Lin does not cure the deficiencies of WO 98/39000. Lin is directed to compounds that are nicotinic agonists (*see* Lin at Abstract; column 1, lines 5-8; column 6, lines 58-60; column 21, lines 58 to column 22, line 25; column 22, lines 55-62). The invention claimed in the instant application is directed to the use of compounds that are cholinesterase antagonists (i.e., cholinesterase inhibitors). Moreover, Lin's compounds are structurally unrelated to the claimed compounds (i.e., donepezil, compounds of Formula (I)). There is no teaching or suggestion in Lin which would lead one of skill in the art to conclude that the nicotine derivative agonists described therein may be substituted with the cholinesterase antagonists of the instant claims. Lin in combination with WO 98/39000 does not render the claimed invention obvious.

Buccafusco does not cure the deficiencies of WO 98/39000. Buccafusco teaches, *inter alia*, that administering diisopropylfluorophosphate or echothiophate to rats during the induction of morphine dependency resulted in reduction of certain symptoms associated with naloxone precipitated withdrawal..

Diisopropylfluorophosphate and echothiophate are organophosphate compounds. The claimed compounds (i.e., donepezil and the compound of Formula (I)) are not organophosphate compounds and have chemical structures that are unrelated to Buccafusco's compounds. There

is no structural relationship between Buccafusco's compounds and the claimed compounds that would motivate one skilled in the art to select the compounds of the instant claims.

The Examiner's reliance on the mechanism of action is insufficient to support a *prima facie* obviousness rejection. In an unpredictable field like chemistry, one skilled in the art would not expect compounds with completely different structures to have the same activity and mechanisms of action for treating any particular disease or disorder. Compounds with wholly different structures may have some overlapping mechanisms of action; however, a person of skill in the art would also expect the compounds to possess other mechanisms of action that would have an impact on their ability to treat a particular disease or disorder. There is no evidence that the results achieved using diisopropylfluorophosphate and echothiophate, as described by Buccafusco, would be predictive of successful results for every single cholinesterase inhibitor known in the art. Accordingly, one skilled in the art would not be motivated to select the compounds of the instant claims.

Moreover, the compounds described in Buccafusco do not achieve the same anti-withdrawal effect that the Examiner is relying on for the obviousness rejection. For example, Buccafusco states that the "apparent anti-withdrawal effect of DFP [diisopropylfluorophosphate] was not reproduced by the selective peripherally acting AChE [acetylcholinesterase] inhibitor, echothiophate ... ." *See* Buccafusco at Abstract, lines 10-11. Buccafusco further states that "[t]he selective peripherally acting organophosphate AChE inhibitor echothiophate was *completely ineffective* in preventing the naloxone-evoked pressor response." (Buccafusco at p. 81, 2^{d} column, 2^{d} full paragraph.) Thus, the anti-withdrawal effects are compound specific, and are not predictable based solely on the purported mechanism of action. Further, Buccafusco does not provide any guidance as to which cholinesterase inhibitors would have effective anti-withdrawal properties and which would not, and as such, fails to provide any motivation or suggestion for one skilled in the art to select, with a reasonable expectation of success, the cholinesterase inhibitors that would be useful in the treatment of substance abuse.

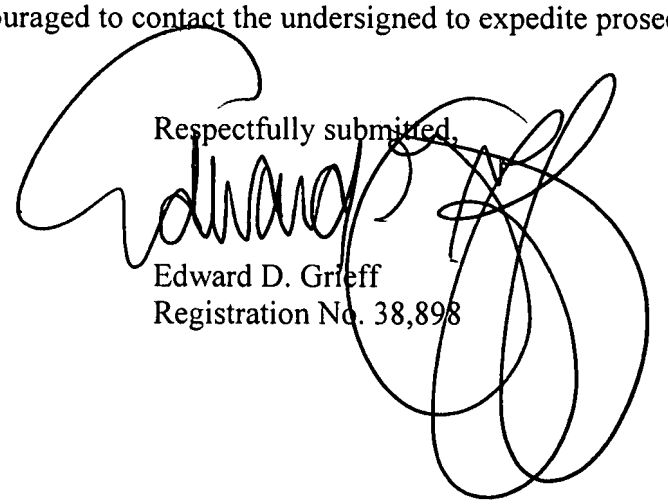
Thus, Buccafusco in combination with WO 98/39000 does not render the claimed invention obvious.

Because neither Lin nor Buccafusco cure the deficiencies of WO 98/39000, Applicants respectfully request that the rejection under 35 USC § 103 be withdrawn.

Conclusion

An early and favorable reconsideration and allowance of claims 25-45 is respectfully requested. The Examiner is encouraged to contact the undersigned to expedite prosecution of this application.

Respectfully submitted,



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